REMARKS

Claims 25-34, 38-63 and 67-71 are pending. Claims 25-34, 38-52 and 56-57 have been withdrawn from examination. Claims 53-55, 58-63 and 67-71 have been examined on the merits. Claim 53 has been amended. The amendment is supported throughout the specification, for example, at page 30, lines 23-29. Accordingly, the amendment raises no issue of new matter. Furthermore, Applicants wish to make clear that the amendment has not been made to obviate the prior art but rather to state that which is self-evident from the specification -- that the claimed "array" results from transfecting with a library of polynucleotides.

Reconsideration of the application is respectfully requested in view of the arguments below.

Rejection under 35 U.S.C. §112, First Paragraph (Written Description)

The rejection of claims 53-55, 58-63 and 67-71 as allegedly failing to comply with the written description requirement is respectfully traversed. According to the Examiner, the claims contain subject matter that is not sufficiently described in the specification to convey that the inventor was in possession of the claimed invention. The Examiner asserts that the specification fails to exemplify a sequence of amino acids that is at least 75% identical to a native immunoglobulin ("Ig") heavy chain, a sequence of 25 consecutive amino acids from the Ig light or heavy chain variable region or a description of any C_HBP array. As best as the Applicants can determine, the rejection seems to be based on the assertion that no complete sequence of a C_HBP is disclosed and that full sequences are essential to enable a genus invention.

The proper standard for determining compliance with the written description requirement of 35 U.S.C. § 112, first paragraph, is whether the specification reasonably conveys to the skilled artisan that the inventor was in possession of the claimed invention as of the filing date. *See* MPEP § 2163.02 (citing *Ralston Purina*

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Co. v. Far-Mar-Co., Inc., 772 F.2d 1570, 227 USPQ 177, 179 (Fed. Cir. 1985)). The subject matter of the claimed invention need not be described literally in the specification in order to satisfy the requirements of 35 U.S.C. § 112, first paragraph. *Id.* The USPTO's approach for evaluating the written description requirement as specified in *Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112 ¶1, "Written Description" Requirement*, states that an adequate written description "may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention." 66 Fed. Reg. 1099, 1105 (2001) (emphasis added).

It is respectfully submitted that the present rejection is based on a flawed approach to evaluate written description of a genus invention as applied in the facts of the instant case. According to the Federal Circuit,

> [p]recedent illustrates that the determination of what is needed to support generic claims to biological subject matter depends on a variety of factors, such as the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, the predictability of the aspect at issue, and other considerations appropriate to the subject matter.

Capon v. Eshhar, 418 F.3d 1349, 1359 (Fed. Cir. 2005) (copy attached). The present rejection, however, fails to properly consider the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, and the predictability of the aspect at issue.

First, the rejection fails to consider that individual C_HBP polypeptides of the claimed array, which comprise a constant region tailpiece of a mu or alpha chain, and a 25 amino acid segment of an Ig light or heavy chain variable region, (the variable region specifically binding to a ligand with a $K_D < 10^{-6}$ moles/liter or forming one or more covalent bonds with one or more polypeptides in the transfected cell

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which together specifically binds to a ligand with a $K_D < 10^{-6}$ moles/liter), are forms of immunoglobulins which are well known in the art.

The allowance for variations in the sequence of the C_HBP polypeptides (i.e., at least 75% identity) acknowledges the well known fact that sequence variation exists and has been readily demonstrated in Ig domains. One skilled in the art can readily use this knowledge in forming the claimed C_HBP arrays. Furthermore, the present application provides numerous amino acid sequences that one skilled in the art can use to make the claimed array. For example, the specification at pages 16-17 and Table 3 provides the mu and alpha tailpiece amino acid sequences from several different species of animal. The function of the tailpiece in polymerizing with J chain is described at page 16 of the specification. Thus, not only are the sequences of the various Ig components well known but the specification provides many of these sequences from which one skilled in the art can use to prepare a suitable C_HBP array in eukaryotic cells.

In addition, the specification at pages 12-16 and Tables 1 and 2 provides amino acid sequences for Ig light and heavy chain variable regions. In particular, the consensus CDR sequences shown in Table 2 are readily useable to prepare sequences which are at least 75% identical to a light or heavy chain variable region and comprise at least 25 consecutive residues. Furthermore, the structure of variable regions of immunoglobulins, like that of the mu and alpha tailpieces, is quite well known as are the methods of sequence variability selection. In this regard, the specification cites at page 15, lines 7-9 to a well known Ig sequence database "Kabat et al., Sequences of Immunological Interest, National Institutes of Health, Bethesda, Md. 1991" and at page 24, lines 11-14 to well known algorithms to determine a percentage of sequence identity.

Because extensive knowledge concerning Ig sequences is resident in the prior art (and disclosed in the specification) and there are many tools and much expertise to prepare with reasonable predictability various recombinant forms of Ig, it must

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be concluded that the selection of an amino acid sequence that is at least 75% identical to 25 consecutive residues of a light or heavy chain variable region is well within the capability of the ordinary skilled artisan and fully contemplated by the inventors, evidencing that they were in full possession of the clamed array.

The statement in the rejection that written description of the claimed C_HBP array requires the specification to describe "the numerous ligands that can bind to the CHBP array such that a specificity of binding of Kd <10-6 is obtained" (Office Action, page 8) also exemplifies a failure to properly evaluate the invention when determining written description. See Capon v. Eshhar, 418 F.3d 1349, 1359 (Fed. Cir. 2005). To determine the affinity of a ligand for a C_HBP (e.g. an antibody) cannot be said to be anything but routine as such determinations with antibodies go back to at least the 1960s. Applicants need not specify all the various ligands that one can make antibodies to since such ligands and antibodies are well known. Obtaining new such antibodies also is routine as exemplified by the prior art and the present rejection offers no evidence to the contrary. Applicants need not specify the various possible sequences or the specific ligands to demonstrate possession of the claimed genus when such information is well known. To demand otherwise evidences a failure to properly consider the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, and the predictability of the aspect at issue.

It is respectfully submitted that written description in the instant case is at least as thorough as in Capon and Eshhar, 418 F.3d 1349 (Fed. Cir. 2005) where the Federal Circuit overturned a rejection for written description affirmed by the Board of Patent Appeals and Interferences (BPAI). The claims of both Capon and Eshhar involve immunoglobulins, specifically, single chain Fv immunoglobulins expressed in cells as a fusion to an endogenous protein. The specification did not disclose the full sequence of the various immunoglobulins and chimeric proteins but

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disclosed procedures for identifying and obtaining them and cited to other sources for the sequences.

> Eshhar's specification contains the nucleotide sequences of sixteen different receptor primers and four different scFv primers from which chimeric genes encoding scFvR may be obtained, while Capon's specification cites literature sources of such information. Eshhar's specification shows the production of chimeric genes encoding scFvR using primers, as listed in Eshhar's Table I. Capon stated that natural genes are isolated and joined using conventional methods, such as the polymerase chain reaction or cloning by primer repair. Capon, like Eshhar, discussed various known procedures for identifying, obtaining, and linking DNA segments, accompanied by experimental examples.

Id. at 1356. The BPAI concluded that the Capon and Eshhar specifications lacked sufficient written description because they did not contain the full sequences of the chimeric proteins.

> The Board stated that "controlling precedent" required inclusion in the specification of the complete nucleotide sequence of "at least one" chimeric gene. Bd. op. at 4. The Board also objected that the claims were broader than the specific examples.

Id. However, the Federal Circuit held that the BPAI, "erred in ruling that §112 imposes a per se rule requiring recitation in the specification of the nucleotide sequence of claimed DNA, when that sequence is already known in the field." *Id.* at 1360.

Applicants respectfully submit that when the instantly claimed invention is properly considered along with the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, and the predictability of the aspect at issue, one must conclude that the written description requirement has been satisfied by the present specification. Accordingly, reconsideration and withdrawal of the rejection is respectfully urged.

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Rejection under 35 U.S.C. §102 (Anticipation)

The rejection of claims 53-55, 58, 63 and 67-71 as allegedly lacking novelty over Ma et al. (Eu J Immunol) is respectfully traversed.

In order to anticipate a claim, a single prior art reference must provide each and every element set forth in the claim. In re Bond, 15 USPQ2d 1566, 1567 (Fed. Cir. 1990). See also, MPEP §2131. The Examiner bears the initial burden of establishing a *prima facie* case of anticipation. Only when a *prima facie* case has been established does the burden shift to the applicant to rebut the *prima facie* case. See, e.g., In re Morris, 127 F.3d 1048, 1054 (Fed. Cir. 1997).

The rejection states that Ma discloses at pages 132-133 twenty two transgenic plants regenerated following transformation with heavy and light chains containing constructs and that this constitutes and array as presently claimed.

Applicant, however, points out that the claimed C_HBP array results from transfecting with a library of polynucleotides. No such library is described anywhere in Ma et al. In all cases, the transformants produced by Ma et al. are obtained by transfecting with a single polynucleotide. The reference, therefore, fails to disclose each and every element of the claims. See In re Bond, 15 USPQ2d 1566, 1567 (Fed. Cir. 1990). See also, MPEP §2131. Reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

Applicants believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

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Atty. Dkt. No. 068904-0507

Respectfully submitted,

Date December 5, 2005

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418 F.3d 1349, 76 U.S.P.Q.2d 1078
(Cite as: 418 F.3d 1349)

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Briefs and Other Related Documents

United States Court of Appeals,Federal Circuit.
Daniel J. **CAPON**, Arthur Weiss, Brian A. Irving, Margo R. Roberts, and Krisztina Zsebo, Appellants,
v.
Zelig **ESHHAR**, Daniel Schindler, Tova Waks, and Gideon Gross, Cross-Appellants,
v.
Jon Dudas, Director of the Patent and Trademark Office, Intervenor.
Nos. 03-1480, 03-1481.

Aug. 12, 2005.

Background: The United States Patent and Trademark Office Board of Patent Appeals and **Interferences** decided in **interference** proceeding that specifications in patents and application did not meet written description requirement and cancelled all of the claims of both parties corresponding to the **interference** count. Parties appealed.

Holdings: The Court of Appeals, Pauline Newman, Circuit Judge, held that:

1(1) nucleotide by nucleotide re-analysis was not required per se to meet written description requirement when structure of component deoxyribonucleic acid (DNA) segments was already known in the field, and

4(2) whether inventors demonstrated sufficient generality to support scope of some or all of their claims had to be determined claim by claim.

Vacated and remanded.

West Headnotes

[1] **Patents 291** 99

291 Patents
291IV Applications and Proceedings Thereon
291k99 k. Description of Invention in Specification. Most Cited Cases
Nucleotide by nucleotide re-analysis was not required per se to meet patent law's written description requirement when structure of component deoxyribonucleic acid (DNA) segments was already known in the field. 35 U.S.C.A. § 112.

[2] **Patents 291** 99

291 Patents
291IV Applications and Proceedings Thereon
291k99 k. Description of Invention in Specification. Most Cited Cases
The written description requirement implements the principle that a patent must describe the technology that is sought to be patented; the requirement serves both to satisfy the inventor's obligation to disclose the technologic knowledge upon which the patent is based, and to demonstrate that the patentee was in possession of the invention that is claimed. 35 U.S.C.A. § 112.

[3] **Patents 291** 99

291 Patents
291IV Applications and Proceedings Thereon
291k99 k. Description of Invention in Specification. Most Cited Cases
In the patent context, the written description requirement must be applied in the context of the particular invention and the state of the knowledge. 35 U.S.C.A. § 112.

[4] **Patents 291** 99

291 Patents
291IV Applications and Proceedings Thereon
291k99 k. Description of Invention in Specification. Most Cited Cases
Whether inventors demonstrated sufficient generality to support scope of some or all of their claims, within the context of the patent law's written description requirement, had to be determined claim by claim with regard to concept of selecting and combining gene sequence which encoded variable domain of antibody and sequence which encoded lymphocyte activation protein, into single deoxyribonucleic acid (DNA) sequence which, upon expression, allowed for immune responses that did not occur in nature. 35 U.S.C.A. § 112.

[5] **Patents 291** 99

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291 Patents
291IV Applications and Proceedings Thereon
291k99 k. Description of Invention in Specification. Most Cited Cases
Within the context of the patent law's written description requirement, in the unpredictable fields of science, it is appropriate to recognize the variability in the science in determining the scope of the coverage to which the inventor is entitled; such a decision usually focuses on the exemplification in the specification. 35 U.S.C.A. § 112.

[6] Patents 291 ⚿99

291 Patents
291IV Applications and Proceedings Thereon
291k99 k. Description of Invention in Specification. Most Cited Cases
For the purpose of the patent law's written description requirement, the determination of what is needed to support generic claims to biological subject matter depends on a variety of factors, such as the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, the predictability of the aspect at issue, and other considerations appropriate to the subject matter. 35 U.S.C.A. § 112.

[7] Patents 291 ⚿99

291 Patents
291IV Applications and Proceedings Thereon
291k99 k. Description of Invention in Specification. Most Cited Cases
It is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention, for the purpose of the patent law's written description requirement. 35 U.S.C.A. § 112.

[8] Patents 291 ⚿99

291 Patents
291IV Applications and Proceedings Thereon
291k99 k. Description of Invention in Specification. Most Cited Cases
While a generic invention requires adequate support, the sufficiency of the support must be determined in the particular case, for the purpose of the patent law's written description requirement. 35 U.S.C.A. § 112.

[9] Patents 291 ⚿99

291 Patents
291IV Applications and Proceedings Thereon
291k99 k. Description of Invention in Specification. Most Cited Cases
The predictability or unpredictability of the science is relevant to deciding how much experimental support is required to adequately describe the scope of an invention, for the purpose of the patent law's written description requirement. 35 U.S.C.A. § 112.

Patents 291 ⚿328(2)

291 Patents
291XIII Decisions on the Validity, Construction, and Infringement of Particular Patents
291k328 Patents Enumerated
291k328(2) k. Original Utility. Most Cited Cases
5,359,046, 6,407,221. Cited.

***1350** Steven B. Kelber, Piper Rudnick, LLP, of Washington, DC, argued for appellants.
Roger L. Browdy, Browdy and Neimark, P.L.L.C., of Washington, DC, argued for cross-appellants.
Mary L. Kelly, Associate Solicitor, Office of the Solicitor, United States Patent and Trademark Office, of Arlington, Virginia, argued for intervenor. With her on the brief were John M. Whealan, Solicitor and Stephen Walsh, Associate Solicitor.

Before NEWMAN, MAYER, FN* and GAJARSA, Circuit Judges.

FN* Haldane Robert Mayer vacated the position of Chief Judge on December 24, 2004.

PAULINE NEWMAN, Circuit Judge.
Both of the parties to a patent interference proceeding have appealed the decision of the Board of Patent Appeals and Interferences of the United States Patent and Trademark Office, wherein the Board held that the specification of neither party met the written description requirement of the patent statute. *Capon v. Eshhar,* Interf. No. 103,887 (Bd. Pat.App. & Interf. Mar. 26, 2003). The Board dissolved the interference and cancelled all of the claims of both parties corresponding to the interference count. With this ruling, the Board terminated the proceeding and did not reach the question of priority of invention. We conclude that the Board erred in its application of the law of written

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description. The decision is vacated and the case is remanded to the Board for further proceedings.

BACKGROUND

Daniel J. **Capon**, Arthur Weiss, Brian A. Irving, Margo R. Roberts, and Krisztina Zsebo (collectively "**Capon**") and Zelig **Eshhar**, Daniel Schindler, Tova Waks, and ***1351** Gideon Gross (collectively "**Eshhar**") were the parties to an **interference** proceeding between **Capon's** United States Patent No. 6,407,221 ("the '221 patent") entitled "Chimeric Chains for Receptor-Associated Signal Transduction Pathways" and **Eshhar's** patent application Serial No. 08/084,994 ("the '994 application") entitled "Chimeric Receptor Genes and Cells Transformed Therewith." **Capon's** Patent No. 5,359,046 ("the '046 patent"), parent of the '221 patent, was also included in the **interference** but was held expired for non-payment of a maintenance fee. The PTO included the '046 patent in its decision and in its argument of this appeal. FN1

> FN1. Although **Capon** is designated as appellant and **Eshhar** as cross-appellant, both appealed the Board's decision. *See* Fed. R.App. P. 28(h). The Director of the PTO intervened to support the Board, and has fully participated in this appeal.

A patent **interference** is an administrative proceeding pursuant to 35 U.S.C. § § 102(g) and 135(a), conducted for the purpose of determining which of competing applicants is the first inventor of common subject matter. An **interference** is instituted after the separate patent applications have been examined and found to contain patentable subject matter. **Capon's** patents had been examined and had issued before this **interference** was instituted, and **Eshhar's** application had been examined and allowed but a patent had not yet issued.

During an **interference** proceeding the Board is authorized to determine not only priority of invention but also to redetermine patentability. 35 U.S.C. § 6(b). The question of patentability of the claims of both parties was raised *sua sponte* by an administrative patent judge during the preliminary proceedings. Thereafter the Board conducted an *inter partes* proceeding limited to this question, receiving evidence and argument. The Board then invalidated all of the claims that had been designated as corresponding to the count of the **interference**, *viz.*, all of the claims of the **Capon** '221 patent, claims 5-8 of the **Capon** '046 patent, and claims 1-7, 9-20, and 23 of the **Eshhar** '994 application.

In accordance with the Administrative Procedure Act, the law as interpreted and applied by the agency receives plenary review on appeal, and the agency's factual findings are reviewed to determine whether they were arbitrary, capricious, or unsupported by substantial evidence in the administrative record. *See* 5 U.S.C. § 706(2); *Dickinson v. Zurko*, 527 U.S. 150, 164-65, 119 S.Ct. 1816, 144 L.Ed.2d 143 (1999); *In re Gartside*, 203 F.3d 1305, 1315 (Fed.Cir.2000).

The Invention

A chimeric gene is an artificial gene that combines segments of DNA in a way that does not occur in nature. The '221 patent and '994 application are directed to the production of chimeric genes designed to enhance the immune response by providing cells with specific cell-surface antibodies in a form that can penetrate diseased sites, such as solid tumors, that were not previously reachable. The parties explain that their invention is a way of endowing immune cells with antibody-type specificity, by combining known antigen-binding-domain producing DNA and known lymphocyte-receptor-protein producing DNA into a unitary gene that can express a unitary polypeptide chain. **Eshhar** summarized the problem to which the invention is directed:

> Antigen-specific effector lymphocytes, such as tumor-specific T cells, are very rare, individual-specific, limited in their recognition spectrum and difficult to obtain against most malignancies. Antibodies, on the other hand, are readily ***1352** obtainable, more easily derived, have wider spectrum and are not individual-specific. The major problem of applying specific antibodies for cancer immunotherapy lies in the inability of sufficient amounts of monoclonal antibodies (mAb) to reach large areas within solid tumors.

Technical Paper Explaining **Eshhar's** Invention, at 6.

The inventions of **Capon** and **Eshhar** are the chimeric DNA that encodes single-chain chimeric proteins for expression on the surface of cells of the immune system, plus expression vectors and cells transformed by the chimeric DNA. The experts for both parties explain that the invention combines selected DNA segments that are both endogenous and

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noncndogenous to a cell of the immune system, whereby the nonendogenous segment encodes the single-chain variable ("scFv") domain of an antibody, and the endogenous segment encodes cytoplasmic, transmembrane, and extracellular domains of a lymphocyte signaling protein. They explain that the scFv domain combines the heavy and light variable ("Fv") domains of a natural antibody, and thus has the same specificity as a natural antibody. Linking this single chain domain to a lymphocyte signaling protein creates a chimeric scFv-receptor ("scFvR") gene which, upon transfection into a cell of the immune system, combines the specificity of an antibody with the tissue penetration, cytokine production, and target-cell destruction capability of a lymphocyte.

The parties point to the therapeutic potential if tumors can be infiltrated with specifically designed immune cells of appropriate anti-tumor specificity.

The Eshhar Claims

The Board held unpatentable the following claims of **Eshhar's** '994 application; these were all of the '994 claims that had been designated as corresponding to the count of the **interference**. **Eshhar's** claim 1 was the designated count.

1. A chimeric gene comprising
a first gene segment encoding a single-chain Fv domain (scFv) of a specific antibody and
a second gene segment encoding partially or entirely the transmembrane and cytoplasmic, and optionally the extracellular, domains of an endogenous protein
wherein said endogenous protein is expressed on the surface of cells of the immune system and triggers activation and/or proliferation of said cells,
which chimeric gene, upon transfection to said cells of the immune system, expresses said scFv domain and said domains of said endogenous protein in one single chain on the surface of the transfected cells such that the transfected cells are triggered to activate and/or proliferate and have MHC nonrestricted antibody-type specificity when said expressed scFV domain binds to its antigen.

2. A chimeric gene according to claim 1 wherein the second gene segment further comprises partially or entirely the extracellular domain of said endogenous protein.

3. A chimeric gene according to claim 1 wherein the first gene segment encodes the scFv domain of an antibody against tumor cells.

4. A chimeric gene according to claim 1 wherein the first gene segment encodes the scFv domain of an antibody against virus infected cells.

5. A chimeric gene according to claim 4 wherein the virus is HIV.

6. A chimeric gene according to claim 1 wherein the second gene segment encodes a lymphocyte receptor chain.

***1353** 7. A chimeric gene according to claim 6 wherein the second gene segment encodes a chain of the T cell receptor.

9. A chimeric gene according to claim 7 wherein the second gene segment encodes the <<alpha>>, <<beta>>, <<gamma>>, or <<delta>> chain of the antigen-specific T cell receptor.

10. A chimeric gene according to claim 1 wherein the second gene segment encodes a polypeptide of the TCR/CD3 complex.

11. A chimeric gene according to claim 10 wherein the second gene segment encodes the zeta or eta isoform chain.

12. A chimeric gene according to claim 1 wherein the second gene segment encodes a subunit of the Fc receptor or IL-2 receptor.

13. A chimeric gene according to claim 12 wherein the second gene segment encodes a common subunit of IgE and IgG binding Fc receptors.

14. A chimeric gene according to claim 13 wherein said subunit is the gamma subunit.

15. A chimeric gene according to claim 13 wherein the second gene segment encodes the CD16<<alpha>> chain of the Fc<<gamma>>RIII or Fc<<gamma>>RII.

16. A chimeric gene according to claim 12 wherein the second gene segment encodes the <<alpha>> or <<beta>> subunit of the IL-2 receptor.

17. An expression vector comprising a chimeric gene according to claim 1.

18. A cell of the immune system endowed with antibody specificity transformed with an expression vector according to claim 17.

19. A cell of the immune system endowed with antibody specificity comprising a chimeric gene according to claim 1.

20. A cell if the immune system according to claim 19 selected from the group consisting of a natural killer cell, a lymphokine activated killer cell, a cytotoxic T cell, a helper T cell and a subtype thereof.

23. A chimeric gene according to claim 1 wherein said endogenous protein is a lymphocyte receptor chain, a polypeptide of the TCR/CD3 complex, or a subunit of the Fc or IL-2 receptor.

The Board did not discuss the claims separately, and held that the specification failed to satisfy the written

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description requirement as to all of these claims.

The Capon Claims

Claims 1-10, all of the claims of the '221 patent, were held unpatentable on written description grounds. Claims 1-6 are directed to the chimeric DNA, claims 7, 8, and 10 to the corresponding cell comprising the DNA, and claim 9 to the chimeric protein:

1. A chimeric DNA encoding a membrane bound protein, said chimeric DNA comprising in reading frame:
DNA encoding a signal sequence which directs said membrane bound protein to the surface membrane;
DNA encoding a non-MHC restricted extracellular binding domain which is obtained from a single chain antibody that binds specifically to at least one ligand, wherein said at least one ligand is a protein on the surface of a cell or a viral protein;
DNA encoding a transmembrane domain which is obtained from a protein selected from the group consisting of CD4, CD8, immunoglobulin, the CD3 zeta chain, the CD3 gamma chain, the CD3 delta chain and the CD3 epsilon chain; and
DNA encoding a cytoplasmic signal-transducing domain of a protein that activates an intracellular messenger system which is obtained from CD3 zeta,
*1354 wherein said extracellular domain and said cytoplasmic domain are not naturally joined together, and said cytoplasmic domain is not naturally joined to an extracellular ligand-binding domain, and when said chimeric DNA is expressed as a membrane bound protein in a host cell under conditions suitable for expression, said membrane bound protein initiates signaling in said host cell when said extracellular domain binds said at least one ligand.
2. The DNA of claim 1, wherein said single-chain antibody recognizes an antigen selected from the group consisting of viral antigens and tumor cell associated antigens.
3. The DNA of claim 2 wherein said single-chain antibody is specific for the HIV env glycoprotein.
4. The DNA of claim 1, wherein said transmembrane domain is naturally joined to said cytoplasmic domain.
5. An expression cassette comprising a transcriptional initiation region, the DNA of claim 1 under the transcriptional control of said transcriptional initiation region, and a transcriptional termination region.
6. A retroviral RNA or DNA construct comprising the expression cassette of claim 5.
7. A cell comprising the DNA of claim 1.
8. The cell of claim 7, wherein said cell is a human cell.
9. A chimeric protein comprising in the N-terminal to C-terminal direction:
a non-MHC restricted extracellular binding domain which is obtained from a single chain antibody that binds specifically to at least one ligand, wherein said at least one ligand is a protein on the surface of a cell or a viral protein;
a transmembrane domain which is obtained from a protein selected from the group consisting CD4, CD8, immunoglobulin, the CD3 zeta chain, the CD3 gamma chain, the CD3 delta chain and the CD3 epsilon chain; and
a cytoplasmic signal-transducing domain of a protein that activates an intracellular messenger system which is obtained from CD3 zeta,
wherein said extracellular domain and said cytoplasmic domain are not naturally joined together, and said cytoplasmic domain is not naturally joined to an extracellular ligand-binding domain, and when said chimeric protein is expressed as a membrane bound protein in a host cell under conditions suitable for expression, said membrane bound protein initiates signaling in said host cell when said extracellular domain binds said at least one ligand.
10. A mammalian cell comprising as a surface membrane protein, the protein of claim 9.

In addition, claims 5, 6, 7, and 8 of **Capon's** '046 patent were held unpatentable. These claims are directed to chimeric DNA sequences where the encoded extracellular domain is a single-chain antibody containing ligand binding activity.

The Board Decision

The Board presumed enablement by the specifications of the '221 patent and '994 application of the full scope of their claims, and based its decision solely on the ground of failure of written description. The Board held that neither party's specification provides the requisite description of the full scope of the chimeric DNA or encoded proteins, by reference to knowledge in the art of the "structure, formula, chemical name, or physical properties" of the DNA or the proteins. In the Board's words:
*1355 We are led by controlling precedent to understand that the full scope of novel chimeric DNA the parties claim is not described in their specifications under 35 U.S.C. § 112, first paragraph, by reference to contemporary and/or prior knowledge in the art of the structure, formula, chemical name, or physical properties of many protein domains, and/or DNA sequences which encode many protein

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domains, which comprise single-chain proteins and/or DNA constructs made in accordance with the plans, schemes, and examples thereof the parties disclose.

Bd. op. at 4. As controlling precedent the Board cited *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559 (Fed.Cir.1997); *Fiers v. Revel*, 984 F.2d 1164 (Fed.Cir.1993); *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200 (Fed.Cir.1991); and *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 296 F.3d 1316 (Fed.Cir.2002). The Board summarized its holding as follows:Here, both **Eshhar** and **Capon** claim novel genetic material described in terms of the functional characteristics of the protein it encodes. Their specifications do not satisfy the written description requirement because persons having ordinary skill in the art would not have been able to visualize and recognize the identity of the claimed genetic material without considering additional knowledge in the art, performing additional experimentation, and testing to confirm results.

Bd. op. at 89.

DISCUSSION

[1] **Eshhar** and **Capon** challenge both the Board's interpretation of precedent and the Board's ruling that their descriptions are inadequate. Both parties explain that their chimeric genes are produced by selecting and combining known heavy- and light-chain immune-related DNA segments, using known DNA-linking procedures. The specifications of both parties describe procedures for identifying and obtaining the desired immune-related DNA segments and linking them into the desired chimeric genes. Both parties point to their specific examples of chimeric DNA prepared using identified known procedures, along with citation to the scientific literature as to every step of the preparative method.

The parties presented expert witnesses who placed the invention in the context of prior knowledge and explained how the descriptive text would be understood by persons of skill in the field of the invention. The witnesses explained that the principle of forming chimeric genes from selected segments of DNA was known, as well as their methods of identifying, selecting, and combining the desired segments of DNA. Dr. **Eshhar** presented an expert statement wherein he explained that the prior art contains extensive knowledge of the nucleotide structure of the various immune-related segments of DNA; he stated that over 785 mouse antibody DNA light chains and 1,327 mouse antibody DNA heavy chains were known and published as early as 1991. Similarly **Capon's** expert Dr. Desiderio discussed the prior art, also citing scientific literature:
The linker sequences disclosed in the '221 patent (col. 24, lines 4 and 43) used to artificially join a heavy and light chain nucleic acid sequence and permit functional association of the two ligand binding regions were published by 1990, as were the methods for obtaining the mature sequences of the desired heavy and light chains for constructing a SAb (Exhibit 47, Batra et al., J., Biol. Chem., 1990; Exhibit 48, Bird et al., Science, 1988; Exhibit 50, Huston et al., PNAS, *1356 1988; Exhibit 51, Chaudhary, PNAS, 1990, Exhibit 56, Morrison et al., Science, 1985; Exhibit 53, Sharon et al., Nature 1984).

Desiderio declaration at 4 ¶ 11.

Both parties stated that persons experienced in this field would readily know the structure of a chimeric gene made of a first segment of DNA encoding the single-chain variable region of an antibody, and a second segment of DNA encoding an endogenous protein. They testified that re-analysis to confirm these structures would not be needed in order to know the DNA structure of the chimeric gene, and that the Board's requirement that the specification must reproduce the "structure, formula, chemical name, or physical properties" of these DNA combinations had been overtaken by the state of the science. They stated that where the structure and properties of the DNA components were known, reanalysis was not required.

Eshhar's specification contains the nucleotide sequences of sixteen different receptor primers and four different scFv primers from which chimeric genes encoding scFvR may be obtained, while **Capon's** specification cites literature sources of such information. **Eshhar's** specification shows the production of chimeric genes encoding scFvR using primers, as listed in **Eshhar's** Table I. **Capon** stated that natural genes are isolated and joined using conventional methods, such as the polymerase chain reaction or cloning by primer repair. **Capon**, like **Eshhar**, discussed various known procedures for identifying, obtaining, and linking DNA segments, accompanied by experimental examples. The Board did not dispute that persons in this field of science could determine the structure or formula of the linked DNA from the known structure or formula of the

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components.

The Board stated that "controlling precedent" required inclusion in the specification of the complete nucleotide sequence of "at least one" chimeric gene. Bd. op. at 4. The Board also objected that the claims were broader than the specific examples. **Eshhar** and **Capon** each responds by pointing to the scientific completeness and depth of their descriptive texts, as well as to their illustrative examples. The Board did not relate any of the claims, broad or narrow, to the examples, but invalidated all of the claims without analysis of their scope and the relation of claim scope to the details of the specifications.

Eshhar and **Capon** both argue that they have set forth an invention whose scope is fully and fairly described, for the nucleotide sequences of the DNA in chimeric combination is readily understood to contain the nucleotide sequences of the DNA components. **Eshhar** points to the general and specific description in his specification of known immune-related DNA segments, including the examples of their linking. **Capon** points similarly to his description of selecting DNA segments that are known to express immune-related proteins, and stresses the existing knowledge of these segments and their nucleotide sequences, as well as the known procedures for selecting and combining DNA segments, as cited in the specification.

Both parties argue that the Board misconstrued precedent, and that precedent does not establish a *per se* rule requiring nucleotide-by-nucleotide re-analysis when the structure of the component DNA segments is already known, or readily determined by known procedures.

The Statutory Requirement

[2] The required content of the patent specification is set forth in Section 112 of Title 35:

§ 112 ¶ 1. The specification shall contain a written description of the invention,*1357 and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The "written description" requirement implements the principle that a patent must describe the technology that is sought to be patented; the requirement serves both to satisfy the inventor's obligation to disclose the technologic knowledge upon which the patent is based, and to demonstrate that the patentee was in possession of the invention that is claimed. *See Enzo Biochem,* 296 F.3d at 1330 (the written description requirement "is the quid pro quo of the patent system; the public must receive meaningful disclosure in exchange for being excluded from practicing the invention for a limited period of time"); *Reiffin v. Microsoft Corp.*, 214 F.3d 1342, 1345-46 (Fed.Cir.2000) (the purpose of the written description requirement "is to ensure that the scope of the right to exclude ... does not overreach the scope of the inventor's contribution to the field of art as described in the patent specification"); *In re Barker*, 559 F.2d 588, 592 n. 4 (CCPA 1977) (the goal of the written description requirement is "to clearly convey the information that an applicant has invented the subject matter which is claimed"). The written description requirement thus satisfies the policy premises of the law, whereby the inventor's technical/scientific advance is added to the body of knowledge, as consideration for the grant of patent exclusivity.

The descriptive text needed to meet these requirements varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence. The law must be applied to each invention that enters the patent process, for each patented advance is novel in relation to the state of the science. Since the law is applied to each invention in view of the state of relevant knowledge, its application will vary with differences in the state of knowledge in the field and differences in the predictability of the science.

For the chimeric genes of the **Capon** and **Eshhar** inventions, the law must take cognizance of the scientific facts. The Board erred in refusing to consider the state of the scientific knowledge, as explained by both parties, and in declining to consider the separate scope of each of the claims. None of the cases to which the Board attributes the requirement of total DNA re-analysis, *i.e., Regents v. Lilly, Fiers v. Revel, Amgen,* or *Enzo Biochem,* require a re-description of what was already known. In *Lilly*, 119 F.3d at 1567, the cDNA for human insulin had never been characterized. Similarly in *Fiers*, 984 F.2d at 1171, much of the DNA sought to be claimed was of unknown structure, whereby this court viewed the breadth of the claims as embracing a "wish" or research "plan." In *Amgen*, 927 F.2d at 1206, the court explained that a novel gene was not

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adequately characterized by its biological function alone because such a description would represent a mere "wish to know the identity" of the novel material. In *Enzo Biochem*, 296 F.3d at 1326, this court reaffirmed that deposit of a physical sample may replace words when description is beyond present scientific capability. In *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1332 (Fed.Cir.2003) the court explained further that the written description requirement may be satisfied "if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure." These evolving principles were applied in *1358 *Noelle v. Lederman*, 355 F.3d 1343, 1349 (Fed.Cir.2004), where the court affirmed that the human antibody there at issue was not adequately described by the structure and function of the mouse antigen; and in *University of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 925-26 (Fed.Cir.2004), where the court affirmed that the description of the COX-2 enzyme did not serve to describe unknown compounds capable of selectively inhibiting the enzyme.

[3] The "written description" requirement must be applied in the context of the particular invention and the state of the knowledge. The Board's rule that the nucleotide sequences of the chimeric genes must be fully presented, although the nucleotide sequences of the component DNA are known, is an inappropriate generalization. When the prior art includes the nucleotide information, precedent does not set a *per se* rule that the information must be determined afresh. Both parties state that a person experienced in the field of this invention would know that these known DNA segments would retain their DNA sequences when linked by known methods. Both parties explain that their invention is not in discovering which DNA segments are related to the immune response, for that is in the prior art, but in the novel combination of the DNA segments to achieve a novel result.

The "written description" requirement states that the patentee must describe the invention; it does not state that every invention must be described in the same way. As each field evolves, the balance also evolves between what is known and what is added by each inventive contribution. Both **Eshhar** and **Capon** explain that this invention does not concern the discovery of gene function or structure, as in *Lilly*. The chimeric genes here at issue are prepared from known DNA sequences of known function. The Board's requirement that these sequences must be analyzed and reported in the specification does not add descriptive substance. The Board erred in holding that the specifications do not meet the written description requirement because they do not reiterate the structure or formula or chemical name for the nucleotide sequences of the claimed chimeric genes.

Claim Scope

[4] There remains the question of whether the specifications adequately support the breadth of all of the claims that are presented. The Director argues that it cannot be known whether all of the permutations and combinations covered by the claims will be effective for the intended purpose, and that the claims are too broad because they may include inoperative species. The inventors say that they have provided an adequate description and exemplification of their invention as would be understood by persons in the field of the invention. They state that biological properties typically vary, and that their specifications provide for evaluation of the effectiveness of their chimeric combinations.

[5] It is well recognized that in the "unpredictable" fields of science, it is appropriate to recognize the variability in the science in determining the scope of the coverage to which the inventor is entitled. Such a decision usually focuses on the exemplification in the specification. *See, e.g., Enzo Biochem*, 296 F.3d at 1327-28 (remanding for district court to determine "[w]hether the disclosure provided by the three deposits in this case, coupled with the skill of the art, describes the genera of claims 1-3 and 5"); *Lilly*, 119 F.3d at 1569 (genus not described where "a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus" had not been provided); *In re Gosteli*, 872 F.2d 1008, 1012 (Fed.Cir.1989) (two chemical compounds were insufficient *1359 description of subgenus); *In re Smith*, 59 C.C.P.A. 1025, 458 F.2d 1389, 1394-95 (1972) (disclosure of genus and one species was not sufficient description of intermediate subgenus); *In re Grimme*, 47 C.C.P.A. 785, 274 F.2d 949, 952 (1960) (disclosure of single example and statement of scope sufficient disclosure of subgenus).

[6] Precedent illustrates that the determination of what is needed to support generic claims to biological subject matter depends on a variety of factors, such as the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, the predictability of the aspect at issue, and other considerations appropriate to the subject matter. *See, e.g., In re Wallach*, 378 F.3d

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1330, 1333-34 (Fed.Cir.2004) (an amino acid sequence supports "the entire genus of DNA sequences" that can encode the amino acid sequence because "the state of the art has developed" such that it is a routine matter to convert one to the other); *University of Rochester*, 358 F.3d at 925 (considering whether the patent disclosed the compounds necessary to practice the claimed method, given the state of technology); *Singh v. Brake*, 317 F.3d 1334, 1343 (Fed.Cir.2003) (affirming adequacy of disclosure by distinguishing precedent in which the selection of a particular species within the claimed genus had involved "highly unpredictable results").

[7] [8] It is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention. *See In re Angstadt*, 537 F.2d 498, 504 (CCPA 1976) ("The examples, both operative and inoperative, are the best guidance this art permits, as far as we can conclude from the record"). While the Board is correct that a generic invention requires adequate support, the sufficiency of the support must be determined in the particular case. Both **Eshhar** and **Capon** present not only general teachings of how to select and recombine the DNA, but also specific examples of the production of specified chimeric genes. For example, **Eshhar** points out that in Example 1 of his specification the FcR<<gamma>> chain was used, which chain was amplified from a human cDNA clone, using the procedure of Kuster, H. et al., J. Biol. Chem., 265:6448-6451 (1990), which is cited in the specification and reports the complete sequence of the FcR<<gamma>> chain. **Eshhar's** Example 1 also explains the source of the genes that provide the heavy and light chains of the single chain antibody, citing the PhD thesis of Gideon Gross, a co-inventor, which cites a reference providing the complete sequence of the Sp6 light chain gene used to construct the single-chain antibody. **Eshhar** states that the structure of the Sp6 heavy chain antibody was well known to those of skill in the art and readily accessible on the internet in a database as entry EMBL:MMSP6718. Example 5 at page 54 of the **Eshhar** specification cites Ravetch et al., J. Exp. Med., 170:481-497 (1989) for the method of producing the CD16<<alpha>> DNA clone that was PCR amplified; this reference published the complete DNA sequence of the CD16<<alpha>> chain, as discussed in paragraph 43 of the **Eshhar** Declaration. Example 3 of the **Eshhar** specification uses the DNA of the monoclonal anti-HER2 antibody and states that the N29 hybridoma that produces this antibody was deposited with the Collection Nationale de Cultures de Microorganismes, Institut Pasteur, Paris, on August 19, 1992, under Deposit No. CNCM I-1262. It is incorrect to criticize the methods, examples, and referenced prior art of the **Eshhar** specification as but "a few PCR primers and probes," as does the Director's brief.

*1360 **Capon's** Example 3 provides a detailed description of the creation and expression of single chain antibody fused with T-cell receptor zeta chain, referring to published vectors and procedures. **Capon**, like **Eshhar**, describes gene segments and their ligation to form chimeric genes. Although **Capon** includes fewer specific examples in his specification than does **Eshhar**, both parties used standard systems of description and identification, as well as known procedures for selecting, isolating, and linking known DNA segments. Indeed, the Board's repeated observation that the full scope of all of the claims appears to be "enabled" cannot be reconciled with the Board's objection that only a "general plan" to combine unidentified DNA is presented. *See In re Wands*, 858 F.2d 731, 736-37 (Fed.Cir.1988) (experimentation to practice invention must not be "undue" for invention to be considered enabled).

The PTO points out that for biochemical processes relating to gene modification, protein expression, and immune response, success is not assured. However, generic inventions are not thereby invalid. Precedent distinguishes among generic inventions that are adequately supported, those that are merely a "wish" or "plan," the words of *Fiers v. Revel*, 984 F.2d at 1171, and those in between, as illustrated by *Noelle v. Lederman*, 355 F.3d at 1350; the facts of the specific case must be evaluated. The Board did not discuss the generic concept that both **Capon** and **Eshhar** described the concept of selecting and combining a gene sequence encoding the variable domain of an antibody and a sequence encoding a lymphocyte activation protein, into a single DNA sequence which, upon expression, allows for immune responses that do not occur in nature. The record does not show this concept to be in the prior art, and includes experimental verification as well as potential variability in the concept.

Whether the inventors demonstrated sufficient generality to support the scope of some or all of their claims, must be determined claim by claim. The Board did not discuss the evidence with respect to the generality of the invention and the significance of the specific examples, instead simply rejecting all the claims for lack of a complete chimeric DNA

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sequence. As we have discussed, that reasoning is inapt for this case. The Board's position that the patents at issue were merely an "invitation to experiment" did not distinguish among the parties' broad and narrow claims, and further concerns enablement more than written description. *See Adang v. Fischhoff*, 286 F.3d 1346, 1355 (Fed.Cir.2002) (enablement involves assessment of whether one of skill in the art could make and use the invention without undue experimentation); *In re Wright*, 999 F.2d 1557, 1561 (Fed.Cir.1993) (same). Although the legal criteria of enablement and written description are related and are often met by the same disclosure, they serve discrete legal requirements.

[9] The predictability or unpredictability of the science is relevant to deciding how much experimental support is required to adequately describe the scope of an invention. Our predecessor court summarized in *In re Storrs*, 44 C.C.P.A. 981, 245 F.2d 474, 478 (1957) that "[i]t must be borne in mind that, while it is necessary that an applicant for a patent give to the public a complete and adequate disclosure in return for the patent grant, the certainty required of the disclosure is not greater than that which is reasonable, having due regard to the subject matter involved." This aspect may warrant exploration on remand.

In summary, the Board erred in ruling that § 112 imposes a *per se* rule requiring recitation in the specification of the nucleotide*1361 sequence of claimed DNA, when that sequence is already known in the field. However, the Board did not explore the support for each of the claims of both parties, in view of the specific examples and general teachings in the specifications and the known science, with application of precedent guiding review of the scope of claims.

We remand for appropriate further proceedings.

VACATED AND REMANDED

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Briefs and Other Related Documents (Back to top)

- 03-1481 (Docket) (May. 27, 2003)
- 03-1480 (Docket) (May. 22, 2003)

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